

# Hypotension, persistent ductus arteriosus and the underlying adrenal insufficiency in low gestation newborns

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Review article

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Recently, there has been increasing awareness of adrenal exhaustion/immuno-endocrine derangements in the chronically ill patients receiving intensive care. Hypotension refractory to the administration of fluid and vasopressors is frequently encountered. In low gestation newborns, the administration of hydrocortisone has been associated with improved hemodynamic stability. To gain an insight into the underlying mechanism of this phenomenon, the relevant literature from a combined search through MEDLINE and EMBASE was examined. Available evidence suggests that adrenal insufficiency/exhaustion in low gestation newborns may be a principal underlying factor for persistent ductus arteriosus and low systemic blood pressure that is unresponsive to vasopressor treatment. It is hypothesized that early postnatal hydrocortisone supplement would facilitate immuno-endocrine homeostasis and the attainment of hemodynamic stability, thereby minimizing the morbidity and mortality associated with inadequate perfusion in this extremely vulnerable population.

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## Hypotension

Adrenal exhaustion/immuno-endocrine derangements in the chronically ill adult patients receiving intensive care have been the subject of recent literature review in endocrinology and critical care medicine.<sup>[1,2]</sup> Although chronic adrenal insufficiency is characterized by decreased systemic vascular resistance and depressed myocardial contractility, acute adrenal insufficiency is associated with variable presentations. Thus, patients with hypotension may appear to have hypovolemic or hyperdynamic shock with associated laboratory findings of eosinophilia, lymphocytosis, hyponatremia (usually related to increased release of vasopressin), hyperkalemia, and hypoglycemia.<sup>[1]</sup> This has heightened our awareness of the existence of similar derangements in extreme premature newborns as the typical pressor-resistant hypotension that occurs in adult ICU patients is frequently seen in Neonatal Intensive Care setting. Most signs and symptoms of adrenal insufficiency are nonspecific and easily masked by critical illness, and hypotension refractory to fluid administration is a common presentation.<sup>[3]</sup> Specifically in the newborn, the neonatal cardiovascular system may be more dependent on the stress response and sympathetic stimulation that enhances neonatal myocardial performance for hemodynamic stability. The administration of opiates predisposes low gestation newborns to decreases in systemic blood pressure by attenuating the stress response and sympathetic stimulation.<sup>[4]</sup> While the hemodynamic stability in the low gestation newborn is dependent on sympathetic drive, their sympathetic response may be limited by inadequate adrenoceptor density. A positive linear relationship between gestational age and the number of adrenoceptors on lymphocytes has been documented.<sup>[5]</sup> Furthermore, there is accumulating evidence that down-regulation of cardiovascular adrenoceptors and second messenger systems through lysosomal destruction contributes to the attenuated cardiovascular

responsiveness to catecholamines seen in severe illness and/or after prolonged vasopressor treatment. Reversal of this process, therefore, requires new protein synthesis and new receptor generation.<sup>[6,7]</sup> Because the expression of the cardiovascular adrenergic receptors and some components of their second messenger systems are inducible by glucocorticoids and thyroid hormones,<sup>[8,9]</sup> adrenal and thyroid insufficiency in prolonged critical illness may play a significant role in the development of pressor-inotrope resistance.<sup>[10-12]</sup> During the period of critical illness, even a relative adrenal insufficiency may cause a disruption in the balance between adrenoceptor destruction and synthesis, leading to decreased sensitivity of the cardiovascular system to endogenous and exogenous catecholamines.<sup>[13]</sup> While the definition of hypotension in low gestation newborns is still controversial, the dramatic effects of hydrocortisone administration in increasing systemic blood pressure in the situation of decreased systemic blood pressure unresponsive to pressor and volume administration has been recognized since 1989.<sup>[13-18]</sup> The increase in systemic blood pressure after corticosteroid administration is thought to be mediated by both non-genomic and genomic actions of the steroid. The non-genomic action of corticosteroids acts by inhibiting catechol-O-methyltransferase, the rate-limiting enzyme in catecholamine metabolism, and decreasing the re-uptake of noradrenaline by sympathetic nerve endings. This results in an increase in the concentration of catecholamines at their receptor sites and an increase in systemic blood pressure.<sup>[19]</sup> Physiologic doses of mineralocorticoids and, to a lesser degree, pharmacologic doses of glucocorticoids also instantly increase cytosolic calcium availability in myocardial and vascular smooth muscle cells,<sup>[19,20]</sup> enhancing myocardial and vascular smooth muscle contractility. The genomic action of glucocorticoids acts by stimulation of synthesis and membrane-assembly of new receptor proteins, thereby increasing beta-adrenoceptor density which mediates an increase in the responsiveness to catecholamines. As a result, systemic blood pressure is increased a few hours after glucocorticoid administration.<sup>[21-23]</sup> It has been speculated that the non-genomic actions of hydrocortisone (which has both mineralocorticoid and glucocorticoid activity) may be responsible for the observed rapid cardiovascular response, whereas the genomic actions contribute to the sustained normalization of blood pressure and the decrease in pressor and inotrope requirements.<sup>[13]</sup> Corticosteroid administration may also increase the effective circulating

blood volume by improving capillary integrity when there is capillary leak.<sup>[24]</sup> Low gestation newborns, however, have a limited cortisol response to stress and ACTH stimulation, and a high plasma concentration ratio of cortisol precursor (17-hydroxyprogesterone) to cortisol, a phenomenon consistent with the adrenal structural and functional immaturity in extreme prematurity.<sup>[5,11,25-27]</sup> Therefore, functional adrenal failure/adrenal exhaustion similar to that seen in adults may occur sooner in low gestation newborns, resulting in immature adrenal glands with a reduced capacity for cortisol biosynthesis.

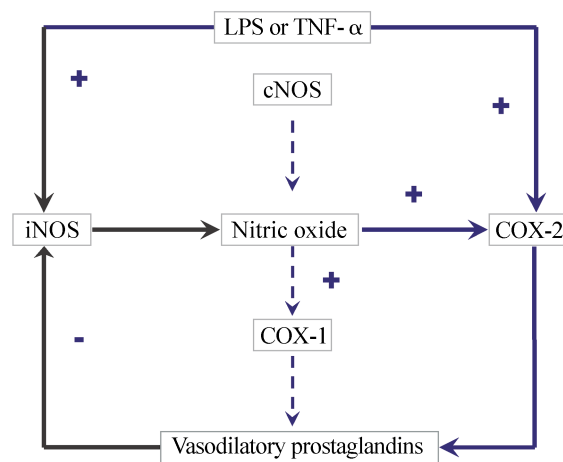
### The ductus arteriosus

As well as the vasoconstrictive response to catecholamines, systemic blood pressure of the low gestation newborn is also influenced by the diameter of the ductus arteriosus. A large diameter ductus arteriosus allows a large shunt of blood out of the systemic circulation through the ductus arteriosus, altering blood-flow distribution. The caliber of the ductus arteriosus may, in turn, be influenced by adrenal insufficiency/exhaustion. In 125 newborns of gestational age of  $28 \pm 2.2$  weeks (mean  $\pm$  SD), of whom none received antenatal steroids and 68% received pulmonary surfactant, serum cortisol concentrations decreased more significantly after postnatal day 2 in infants whose persistent ductus arteriosus (PDA) required treatment (46%) than in those whose PDA did not require treatment ( $P < 0.01$ ).<sup>[28]</sup> The effect of glucocorticoid or cortisol deficiency on the diameter of the ductus arteriosus may be indirect, and through the activity of inducible nitric oxide synthase (iNOS), an enzyme whose expression in the ductus arteriosus in the basal state has been shown to be developmentally regulated.<sup>[29]</sup> Evidence shows that nitric oxide (NO) plays a significant role in the regulation of the calibre of the aorta, pulmonary artery and ductus arteriosus in utero.<sup>[29-33]</sup> NO is synthesized from L-arginine by enzyme nitric oxide synthase (NOS). There are two isoforms: constitutive cNOS and inducible iNOS. cNOS releases NO in the vascular endothelium and the central nervous system and is responsible for the effects attributable to Endothelium-Derived Relaxing Factor.<sup>[34]</sup> It is generally thought that the expression of the iNOS isoform is stimulated and regulated in many cell types including macrophages, neutrophils, endothelial and smooth muscle cells at the transcription level by lipopolysaccharide (LPS) and a number of pro-inflammatory cytokines.<sup>[35-39]</sup>

Once expressed, this isoform can generate nanomolar amounts of NO for hours or days and exerts a prolonged and more profound effect on vascular tone.<sup>[40-43]</sup> NO synthesis, however, has been shown to increase during normal pregnancy in the rat and iNOS has been implicated as a source of NO in the utero-placental unit.<sup>[44]</sup> In contrast to an untreated group of rats as controls, the rats in the last week of pregnancy were given (1) a 5-day intraperitoneal treatment of L-N<sup>G</sup>-(1-iminoethyl)lysine at doses of 1, 10, and 100 µg/ml in their drinking water to selectively inhibit iNOS activity; (2) LPS at 30 µg/kg body weight to stimulate iNOS production of NO; and (3) sodium nitroprusside at 10 µg·kg<sup>-1</sup>·min<sup>-1</sup> as a NO-donor to increase serum NO concentration. Bustamante et al<sup>[45]</sup> documented on a computer-generated three-dimensional image the positive evidence of iNOS gene expression by the polymerase chain reaction method in the placenta and fetal heart central vessels in the untreated (control) group, the significant constriction of the great vessels and the ductus arteriosus with the administration of iNOS-inhibitor ( $P<0.001$ ), and the significant dilatation after the administration of both LPS and NO-donor ( $P<0.05$ ). The fetal great vessel vasorelaxation induced by LPS is reduced by the administration of iNOS-inhibitor ( $P<0.001$ ). These investigators have concluded that iNOS is expressed in a sustained manner in the fetus and suggested that NO derived from iNOS is important in the maintenance of the caliber of the fetal great vessels in the normal state. Subsequently, Clyman et al<sup>[29]</sup> reported the expression of iNOS in the luminal endothelial cells of the ovine fetal ductus and aorta. The ductus arteriosus rings from the fetuses <72% gestation were more sensitive to the vasorelaxant effect of NO than those from the fetuses >86% gestation ( $P<0.01$ ) under the same experimental conditions. Of relevance to neonatal intensive care practice is that an estimated 45% of fetuses delivered after preterm labor has been exposed to low grade ascending infection.<sup>[46]</sup> The incidence of ascending infection increases with decreasing length of gestation and may be a major cause of preterm labor before 30 weeks of gestation.<sup>[47]</sup> Matsuoka et al<sup>[48]</sup> have reported increased cord blood pro-inflammatory cytokine-producing lymphocytes in newborns with intrauterine infection. Since cortisol modulates pro-inflammatory cytokine production, failure of suppression of pro-inflammatory cytokine production secondary to adrenal insufficiency of prematurity would result in up-regulation of NO production by iNOS and enhance the dilatory force on the ductus arteriosus in the low gestation newborn, maintaining the PDA.

## Adrenal insufficiency

Although the role of vasodilatory prostaglandins on PDA is better known than NO, they exert a mutually enhancing vasodilatory effect on the ductus arteriosus. Prostaglandins play an important contributory role in inflammatory response. Like NOS, cyclo-oxygenase (COX), the rate-limiting enzyme in prostaglandin synthesis, is also represented by two isoforms, COX-1 and COX-2. Similar to cNOS, COX-1 appears to be maximally expressed under basal condition to function as the "house-keeping" enzyme that is responsible for basal vasodilatory prostaglandin synthesis, whereas COX-2 activity is stimulated in inflammatory processes, resulting in increased prostaglandin production.<sup>[49-52]</sup> LPS as well as a number of pro-inflammatory cytokines have been found to induce both iNOS and COX-2 in several cell types.<sup>[53]</sup> There is a mutual interaction between NO synthase (NOS) and cyclo-oxygenase (COX) systems in both physiologic and pathologic conditions (Fig. 1).<sup>[54]</sup> The resultant elevated concentrations of NO and prostacyclin would then greatly increase the dilatory force on the low gestation ductus arteriosus and maintain the large ductal diameter over a prolonged period of time in an inflammatory response elicited by pathogen invasion. The inhibition of iNOS and COX-2 induction by adrenal corticosteroids and the lack of effect of these hormones on the constitutive isoforms (i.e., cNOS and COX-1) are common features of the two pathways.<sup>[55-57]</sup> In low gestation newborns with adrenal insufficiency, failure of suppression of the "pathologic" production of NO and prostacyclin by iNOS and COX-2, respectively, with consequent persistent ductal dilatation may be



**Fig. 1.** Model for the mutual interactions between NOS and COX systems in physiological (dotted arrows) and pathological conditions (solid arrows) (adapted from reference 54).

anticipated. Inhibition of prostacyclin production with indomethacin, an inhibitor of both COX-1 and COX-2, is an effective means of constricting the ductus arteriosus in most cases; however, failure of ductal closure or ductal re-opening frequently occurs in low gestation infants <28 weeks of gestation.<sup>[58]</sup> The failure of ductal closure and ductal re-opening associated with sepsis would implicate the more fundamental role of adrenal insufficiency than prostacyclin production in the maintenance of ductal patency mediated by iNOS and COX-2 activity. Indeed, Gonzalez et al<sup>[59]</sup> have reported the significant association of PDA and infection in 114 infants of birth weight of 500-1500 g. Of the 114 infants studied, 40 (36%) were diagnosed as having infection, and 38 (33%) both PDA and infection; in 31 of them these two events were temporally related. Most of these 31 episodes of infection temporally related to PDA (77%) preceded the diagnosis of PDA or occurred on the same day. Infants with a proven infection during the first month demonstrated a significantly higher incidence of late PDA (occurring at postnatal age  $\geq 8$  days) than did infants without evidence of infection, independent of birth weight ( $P < 0.025$ ). The rate of PDA closure failure in the 31 infants whose PDA was temporally related to an episode of infection was also significantly higher (21/31, 68%) than that in the 29 infants with PDA but without infection (5/29, 17%,  $P < 0.02$ ). Furthermore, of the 21 infants with failure of PDA closure temporally related to infection, 13 (62%) failed to respond to one or more courses of indomethacin treatment. Serum TNF- $\alpha$  concentrations were increased more significantly ( $P < 0.05$ ) in infants with infection (median=66 pg/ml, range: 11-1280) and in those whose PDA episodes were diagnosed beyond the first postnatal week (median=46 pg/ml, range: <1-1280) than in infants whose PDA episodes were diagnosed during the first postnatal week (median=8 pg/ml, range: <1-208) or in infants whose PDA was not symptomatic (median=6 pg/ml, range: <1-51). These observations clearly demonstrated the association between late episodes of PDA and infection. Infants with a PDA and a temporally related infection had significantly higher concentrations of serum prostaglandin (as measured by their stable metabolite) than did infants with PDA without infection ( $P < 0.05$ ). Although the serum prostaglandin concentrations decreased after indomethacin treatment, they remained significantly elevated. In those infants who had PDA but without infection, the serum concentrations of prostaglandin decreased to levels similar to those of control subjects ( $P < 0.05$ ).<sup>[59]</sup>

## Conclusion

Since muscular constriction and functional closure of the ductus arteriosus depend on a balance between the dilating and the constricting forces on the ductus arteriosus, the ductus arteriosus in the preterm newborn develops less contractile tension than it does at term because of the vasorelaxant effect of increased synthesis and release of endogenous compounds, such as prostacyclin and NO.<sup>[29,60-63]</sup> It is hypothesized that hydrocortisone supplement would modulate pro-inflammatory cytokine production, thus preventing the production of prostacyclin and NO by COX-2 and iNOS, respectively,<sup>[41]</sup> thereby avoiding the pathologic component of the dilatory force on the ductus arteriosus associated with inflammatory responses. Because glucocorticoids are known to inhibit iNOS and COX-2 but not the constitutively expressed eNOS and COX-1,<sup>[64-66]</sup> it is hypothesized that the use of hydrocortisone to minimize the stimulation of iNOS and COX-2 by pro-inflammatory cytokines would be superior to or more effective than indomethacin or ibuprofen, as it targets at the "pathologic" NO and prostaglandin production while leaving the "physiologic" NO and prostaglandin production unaffected.

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